(FILE 'HOME' ENTERED AT 12:08:41 ON 14 SEP 2001)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, CAPLUS, EMBASE' ENTERED AT 12:08:56 ON 14 SEP 2001

L1 634712 S NANOPARTICLE OR NM
L2 6767 S ENDOSOMOLYTIC OR ENDOSOME
L3 328 S L1 AND L2
L4 1971616 S MONOMER OR POLYME?
L5 24 S L4 AND L3
L6 15 DUP REM L5 (9 DUPLICATES REMOVED)
L7 3697 S ORTHO AND ESTER
L8 892 S L7 AND L4
L9 0 S L8 AND L2
L10 124892 S SENSITIVE AND PH
L11 26 S L3 AND L10
L12 14 DUP REM L11 (12 DUPLICATES REMOVED)
L13 2 S ENDOSOMOLYTIC COMPOUND OR ENDOSOMOLYTIC POLYMER
L14 513 S L2 AND REVIEW
L15 34 S L14 AND L4
L16 27 DUP REM L15 (7 DUPLICATES REMOVED)

L6 ANSWER 11 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999032882 EMBASE
TI Gene transfer with synthetic virus-like particles via the integrin-mediated endocytosis pathway.
AU Erbacher P.; Remy J.-S.; Behr J.-P.
CS J.-P. Behr, UMR 7514 CNRS, Faculte de Pharmacie, Universite Louis Pasteur Strasbourg, BP 24, F-67401 Illkirch, France
SO Gene Therapy, (1999) 6/1 (138-145).
Refs: 64
ISSN: 0969-7128 CODEN: GETHEC
CY United Kingdom
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB The interaction between cationic DNA-containing particles and cell surface anionic proteoglycans is an efficient means of entering cultured cells. Therapeutic in vivo gene delivery levels, however, require binding to less ubiquitous molecules. In an effort to follow adenovirus, thiol-derivatized polyethylenimine (PEI) was conjugated to the integrin-binding peptide CYGGRGDTP via a disulfide bridge. The most extensively conjugated derivative (5.5% of the PEI amine functions) showed physical properties of interest for systemic gene delivery. In the presence of excess PEI-RGD, plasmid DNA was condensed into a rather homogeneous population of 30-100 ***nm*** toroidal particles as by electron microscopy images in 150 mM salt. Their surface charge was close to neutrality as a consequence of the shielding effect of the prominent zwitterionic peptide residues. Transfection efficiency of integrin-expressing epithelial (HeLa) and fibroblast (MRC5) cells was increased by 10- to 100-fold as compared with PEI, even in serum. This large enhancement factor was lost when aspartic acid was replaced by glutamic acid in the targeted peptide sequence (RGD/RGE), confirming the involvement of integrins in transfection. PEI-RGD/DNA complexes thus share with adenovirus constitutive properties

such as size and a centrally protected DNA core, and 'early' properties, ie cell entry mediated by integrins and acid-triggered ***endosome*** escape.

L6 ANSWER 10 OF 15 MEDLINE DUPLICATE 4
AN 2000083589 MEDLINE
DN 20083589 PubMed ID: 10617299
TI Pharmaceutical and biological properties of poly(amino acid)/DNA polyplexes.
AU Lucas P; Milroy D A; Thomas B J; Moss S H; Pouton C W
CS Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, UK.
SO JOURNAL OF DRUG TARGETING, (1999) 7 (2) 143-56.
Journal code: B3S; 9312476. ISSN: 1061-186X.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000202
AB Physicochemical properties of polyplexes formed between pRSVlacZ and poly(amino acid)s were investigated as a paradigm of more complex, synthetic virus-like, DNA delivery systems, that are of interest to many gene delivery laboratories. We observed the interaction between ***polymer*** and DNA using ethidium exclusion, and determined the size distributions and the zeta potentials of polyplexes. We correlated these properties with their fundamental interactions with cultured B16 murine melanoma cells, and the resulting efficiency of transfection. A variety of poly(amino acid)s each condensed DNA to produce particles with mean hydrodynamic diameters of approximately 100 ***nm*** (a typical span of a population was 80-120nm). Poly(amino acid) polyplexes were unstable in electrolyte solutions such as cell culture media. The apparent particle size increased in electrolyte, depending on the charge ratio, to diameters up to 700 ***nm*** . This was thought to be due to aggregation, since neutral particles were most sensitive. When the charge ratio (+/-) exceeded unity polyplexes had positive zeta potentials (which peaked at approximately +30 mV), bound non-specifically to cells, were internalised and in the presence of an ***endosomolytic*** agent were able to transfect cells. Though all cationic poly(amino acid)s investigated formed polyplexes with similar physical properties, their biological properties were significantly different. Polyplexes prepared with poly-L-ornithine were the most effective transfection agents, but poly(lys-co-ala, 1: 1) systems appeared to be inactive. This may reflect the differences in uncoupling of DNA and ***polymer*** , which is expected to be necessary for passage through the nuclear pore. Uncoupling of polycation and DNA was investigated by exposing the complexes to dextran sulphate. Release of DNA was detected by increased fluorescence at 600 ***nm*** in the presence of ethidium. Release of DNA was incomplete from polyplexes formed with high molecular weight polylysine. This may explain the lower levels of transfection observed with high molecular weight polylysine. The significance of these observations for design of advanced non-viral gene delivery systems is discussed.

still increased in efficacy when chloroquine was included.

L6 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2001 ACS
AN 1999:390393 CAPLUS
DN 131:40529
TI In situ formation of particulate complexes of polycations and nucleic acids for delivery to animal cells
IN Behr, Jean-Paul; Blessing, Thomas; Wagner, Ernst; Schuller, Susanne
PA Boehringer Ingelheim International GmbH, Germany; Universite Louis Pasteur de Strasbourg
SO PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

L6 ANSWER 8 OF 15 MEDLINE DUPLICATE 3
AN 2001030037 MEDLINE
DN 20450761 PubMed ID: 10995206
TI pH-sensitive cationic ***polymer*** gene delivery vehicle: N-Ac-poly(L-histidine)-graft-poly(L-lysine) comb shaped ***polymer*** .
AU Benns J M; Choi J S; Mahato R I; Park J S; Kim S W
CS Center for Controlled Chemical Delivery, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, Utah 84112, USA.
SO BIOCONJUGATE CHEMISTRY, (2000 Sep-Oct) 11 (5) 637-45.
Journal code: A1T. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121
AB Advancing biotechnology spurs the development of new pharmaceutically engineered gene delivery vehicles. Poly(L-histidine) PLH has been shown to induce membrane fusion at endosomal pH values, whereas PLL has a well documented efficacy in polyplex formation. Therefore, N-Ac-poly(L-histidine)-graft-poly(L-lysine) PLH-g-PLL was synthesized by grafting poly(L-histidine) to poly(L-lysine) PLL . PLH-g-PLL formed polyplex particles by electrostatic interactions with plasmid DNA pDNA . The mean particle size of the polyplexes was in the range of 117 +/- 6 ***nm*** to 306 +/- 77 ***nm*** . PLH-g-PLL gene carrier demonstrated higher transfection efficacy in 293T cells than PLL at all equivalent weight ratios with pDNA. The inclusion of chloroquine as an ***endosomolytic*** agent enhanced transfection for both PLL and PLH-g-PLL gene carriers. PLH-g-PLL enhanced beta-galactosidase expression compared to PLL, but still increased in efficacy when chloroquine was included.

L6 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2001 ACS
AN 2001:404575 CAPLUS
DN 135:157526
TI Poly(Amidoamine)s as Potential Nonviral Vectors: Ability to Form Interpolyelectrolyte Complexes and to Mediate Transfection in Vitro
AU Richardson, Simon C. W.; Pattrick, Nicola G.; Man, Y. K. Stella; Ferruti, Paolo; Duncan, Ruth

CS Centre for Polymer Therapeutics Welsh School of Pharmacy, Cardiff University, Cardiff, CF10 3XF, UK
SO Biomacromolecules (2001), 2(3), 1023-1028
CODEN: BOMAF6; ISSN: 1525-7797
PB American Chemical Society
DT Journal
LA English
AB Poly(amidoamine)s (PAAs) are water-sol. ***polymers*** that display pH-dependent membrane activity. PAAs have the potential to act as a synthetic alternative to fusogenic peptides and thus promote endosomal escape. The purpose of this study was to investigate for the first time whether PAA have the ability to complex DNA, protect it from nuclease degrdn. and to promote transfection in vitro. PAAs ISA 1 (Mn 6900) and ISA 23 (Mn 10 500) and their 2-phenylethylamine contg. analogs ISA 4 and ISA 22 (Mn .apprx.8000) were studied. All PAAs retarded the electrophoretic mobility of .lambda. Hind III DNA demonstrating interpolyelectrolyte complex (IPEC) formation and toroids of 80-150 ***nm*** in diam. (10:1 ***polymer*** excess) were visible using TEM. DNase II inhibition was obsd. At a ***polymer*** :DNA ratio of 10:1, this was ISA 1(89.6 .+-. 6.1%), ISA 4 (92.2 .+-. 11.2%), ISA 22 (69.4 .+-. 3.7%), and ISA 23 (58.0 .+-. 10.0%). PAAs demonstrated the ability to mediate pSV .beta.-galactosidase transfection of HepG2 cells. At a vector:DNA mass ratio of 5:1, ISA 23 showed equiv. transfection ability compared with polyethylenimine and LipofectIN and was more effective than LipofectACE. These properties suggest that PAAs warrant further development as

L6 ANSWER 1 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001053181 EMBASE
TI ***Polymer*** -based gene delivery with low cytotoxicity by a unique balance of side-chain termini.
AU Putnam D.; Gentry C.A.; Pack D.W.; Langer R.
CS R. Langer, Department of Chemical Engineering, MA Institute of Technology, Cambridge, MA 02139, United States. rlanger@mit.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (30 Jan 2001) 98/3 (1200-1205).
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB Protein expression after delivery of plasmid DNA to the cell nucleus depends on the processes of transcription and translation. Cytotoxic gene-delivery systems may compromise these processes and limit protein expression. This situation is perhaps most prevalent in current nonviral polycationic gene-delivery systems in which the polycationic nature of the delivery system can lead to cytotoxicity. To approach the problem of creating nontoxic but effective gene-delivery systems, we hypothesized that by optimizing the balance between ***polymer*** cationic density with endosomal escape moieties, effective gene transfer with low cytotoxicity could be created. As a model system, we synthesized a series of ***polymers*** whose side-chain termini varied with respect to the balance of cationic centers and endosomal escape moieties. Specifically, by ***polymer*** -analogous amidation we conjugated imidazole groups to the .epsilon.-amines of polylysine in varying mole ratios (73.5 mol % imidazole, 82.5 mol % imidazole, and 86.5 mol % imidazole). The primary

.epsilon.-amine terminus of polylysine served as a model for the cationic centers, whereas the imidazole groups served as a model for the endosomal escape moieties. These ***polymers*** condensed plasmid DNA into nanostructures <150 ***nm*** and possessed little cytotoxicity in vitro. Transfection efficiency, as measured by luciferase protein expression, increased with increasing imidazole content of the ***polymers*** in a nonlinear relationship. The ***polymer*** with the highest imidazole content (86.5 mol %) mediated the highest protein expression, with levels equal to those mediated by polyethylenimine, but with little to no cytotoxicity.

L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1999:625714 CAPLUS
DN 132:26739
TI Poly(amidoamine)s as potential endosomolytic polymers: evaluation in vitro and body distribution in normal and tumor-bearing animals
AU Richardson, S.; Ferruti, P.; Duncan, R.
CS Centre for Polymer Therapeutics, The School of Pharmacy, University of London, London, WC1N 1AX, UK
SO J. Drug Targeting (1999), 6(6), 391-404
CODEN: JDTAEH; ISSN: 1061-186X
PB Harwood Academic Publishers
DT Journal
LA English
AB Fusogenic peptides derived from viral coat proteins cause perturbation of the endosomal membrane and are often used to improve the transfection efficiency of non-viral vectors in vitro. However, fusogenic peptides have limited potential for use in vivo due to their inherent immunogenicity. Totally synthetic polymers that are endosomolytic should circumvent this problem and could be useful as components of non-viral delivery systems as long as they do not immediately localize in the liver after i.v. injection. Linear poly(amidoamine) polymers (PAAs) having amido- and tertiary amino-groups along the main polymer undergo pH-dependent conformational change and thus provide an ideal opportunity for design of polymers that display membrane activity at low pH. Here we describe four PAAs, ISA 1 (Mn = 6900 Da) and ISA 23 (Mn = 10,500 Da) and their analogs ISA 4 and ISA 22 (Mn approx. 8000 Da) contg. approx. 1 mol% 2-p-hydroxyphenylethylamine to allow radioiodination and thus monitoring of their biodistribution. In vitro cytotoxicity was assessed by MTT assay after incubation of PAAs with B16F10 and Mewo cell lines. The IC50 values obsd. for all PAAs were >2 mg/mL in comparison with poly(L-lysine) which displayed an IC50 in the range 0.01 - 0.1 mg/mL. At pH 7.4 none of the PAAs studied was hemolytic at 1 h at concns. below 3 mg/mL. PAAs were subsequently incubated with rat red blood cells for 24h (1 mg/mL) at different pHs. In contrast to poly(L-lysine) which was hemolytic at pH 7.4, 6.5 and 5.5, none of the PAAs was lytic at pH 7.4, but they became membrane active at lower pH (.apprx.45% for ISA 4, 50% for ISA 22 and 90% for ISA 23). These observations were substantiated by SEM and confirm the pH-dependence of membrane activity. After i.v. injection to rats 125I-labeled ISA 4 was immediately taken up by the liver (>80% recovered dose at 1 h) whereas 125I-labeled ISA 22 was not (liver uptake was <10% recovered dose at 5h). Furthermore, biodistribution studies in mice bearing s.c. B16F10 melanoma showed that 125I-labeled ISA 22 was still accumulating in tumor tissue after 5 h (2.5% dose/g). PAAs have potential as endosomolytic agents and quantitation of the endosome to cytoplasm transfer is warranted after i.v. administration.

L16 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 1997:349973 CAPLUS
DN 127:12866
TI The proton sponge: a trick the viruses did not exploit
AU Demeneix, Barbara A.; Behr, Jean Paul
CS Unite de Recherche Associee, Laboratoire de Physiologie Generale et Comparee, Museum National d'Histoire Naturelle, Paris, 75231, Fr.
SO Artif. Self-Assem. Syst. Gene Delivery, Two Conf. (1996), Meeting Date 1995, 146-151. Editor(s): Felgner, Philip L. Publisher: American Chemical Society, Washington, D. C.
CODEN: 64KHA5
DT Conference; General Review
LA English
AB A ***review*** with 18 refs. Several non-permanent polycations possessing substantial buffering capacity below physiol. pH, such as lipopolyamines and polyethylenimines, are efficient transfection agents per se, i.e. without the addn. of lysosomotropic bases, or cell targeting or membrane disruption agents. These vectors have been shown to deliver genes as well as oligonucleotides both in vitro and in vivo. Our hypothesis is that their efficiency relies on extensive ***endosome*** swelling and rupture that provides an escape mechanism for the polycation/DNA particles.

L16 ANSWER 21 OF 27 MEDLINE DUPLICATE 5
AN 1998257905 MEDLINE
DN 98257905 PubMed ID: 9595549
TI Cationic lipids, phosphatidylethanolamine and the intracellular delivery of ***polymeric*** , nucleic acid-based drugs (***review***).
AU Hope M J; Mui B; Ansell S; Ahkong Q F
CS Inex Pharmaceuticals Corporation, Burnaby, B.C., Canada.
SO MOLECULAR MEMBRANE BIOLOGY, (1998 Jan-Mar) 15 (1) 1-14. Ref: 82
Journal code: BTQ; 9430797. ISSN: 0968-7688.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199807
ED Entered STN: 19980731
Last Updated on STN: 19980731
Entered Medline: 19980723
AB ***Polymeric*** , nucleic acid drugs must be protected from endogenous nucleases and delivered to target cell nuclei in order to maximize their activity. Constructs expressing therapeutic genes, antisense oligonucleotides and ribozymes can be delivered into cells by viral vectors, but concerns over safety and clinical utility have led to research into the development of alternative, non-viral delivery systems. Antisense and ribozyme drug development has focused upon modifications to the natural oligonucleotide chemistry which make the molecules resistant to nuclease degradation. These novel oligonucleotides cannot be generated by transgenes and must be administered in similar fashion to conventional drugs. However, oligonucleotides cannot cross membranes by passive diffusion and intracellular delivery for these drugs is very inefficient.

Here we ***review*** the recent advances in forming lipid-DNA particles designed to mimic viral delivery of DNA. Most evidence now supports the hypothesis that lipid-DNA drugs enter target cells by endocytosis and disrupt the endosomal membrane, releasing nucleic acid into the cytoplasm. The mechanisms of particle formation and ***endosome*** disruption are not well understood. Cationic lipids are employed to provide an electrostatic interaction between the lipid carrier and polyanionic nucleic acids, and they are critical for efficient packaging of the drugs into a form suitable for systemic administration. However, their role in ***endosome*** disruption and other aspects of successful delivery leading to gene expression or inhibition of mRNA translation are less clear. We discuss the propensity of lipid-nucleic acid particles to undergo lipid mixing and fusion with adjacent membranes, and how phosphatidylethanolamine and other lipids may act as factors capable of disrupting bilayer structure and the endosomal pathway. Finally, we consider the challenges that remain in bringing nucleic acid

L16 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 1998:507894 CAPLUS
DN 129:254215
TI Theory and practice of using polycationic amphiphiles and ***polymers*** for in vitro and in vivo gene transfer
AU Demeneix, B. A.; Goula, D.; Benoist, C.; Remy, J. S.; Behr, J. P.
CS Laboratoire de Physiologie Generale et Comparee, U.R.A.90 CNRS, Museum National d'Histoire Naturelle, Paris, F-75231, Fr.
SO NATO ASI Ser., Ser. H (1998), 105(Gene Therapy), 195-204
CODEN: NASBE4; ISSN: 1010-8793
PB Springer-Verlag
DT Journal; General Review
LA English
AB A ***review*** with 28 refs. The mechanisms underlying the actions of polycationic (as opposed to monocationic) gene transfer vectors is described. Two main types of vectors are examd., polycationic amphiphiles such as DOGS (Transfectam) and Lipofectamine on the one hand and cationic ***polymers*** such as polyethyleneimine on the other hand. The gene transfer performances of these mols. is a function of their DNA condensing capacity, their interactions with anionic proteoglycans of the cell membrane and their capacity to induce ***endosome*** swelling and rupture. The importance of taking into account the overall charge ratio of complexes when carrying out in vitro or in vivo gene transfer is emphasi

L16 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
AN 1999:374469 CAPLUS
DN 131:174881
TI Peptide-based gene delivery
AU Mahato, Ram I.; Monera, Oscar D.; Smith, Louis C.; Rolland, Alain
CS Copernicus Therapeutics Inc, Cleveland, OH, 44106-3052, USA
SO Curr. Opin. Mol. Ther. (1999), 1(2), 226-243
CODEN: CUOTFO; ISSN: 1464-8431
PB Current Drugs Ltd.
DT Journal; General Review
LA English
AB A ***review*** with 147 refs. To achieve effective plasmid-based gene therapy, the control of cellular access and uptake, intracellular trafficking and nuclear retention of plasmids must be achieved.

Inefficient endosomal release, cytoplasmic transport and nuclear entry of plasmids are amongst some of the key limiting factors in the use of plasmids for effective gene therapy. A no. of non-viral gene delivery systems have been designed to overcome these limiting factors. The most common approach to protect and control plasmid distribution is to complex plasmids with cationic lipids or ***polymers*** through electrostatic interactions. Endosomal release of plasmids can be achieved, for instance, by using pH-sensitive lipids, inactivated viral particles, ***endosomolytic*** peptides and ***polymers*** . Among the least explored gene delivery systems are those that consist mainly of synthetic, short peptides. Peptides can be incorporated into multi-component gene delivery complexes for specific purposes, such as for DNA condensation, cell-specific targeting, endosomolysis or nuclear transport. The aims of this ***review*** are to: (i) explore the conceptual and exptl. aspects of peptide-DNA interactions; (ii) critically assess the possible use of peptides for efficient gene transfer; and (iii) present an overview on the use of peptides to enhance the effectiveness of other gene delivery systems. On balance, peptide-based gene delivery systems appear to have a significant potential as com. viable gene delivery products.

R

L16 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

AN 2001:240751 CAPLUS

DN 135:55312

TI Nonviral gene therapy and its delivery systems

AU Ma, Haiching; Diamond, Scott L.

CS Institute for Medicine and Engineering, Department of Chemical Engineering, 1024 Vagelos Research Laboratories, University of Pennsylvania, Philadelphia, PA, 19104, USA

SO Curr. Pharm. Biotechnol. (2001), 2(1), 1-17
CODEN: CPBUBP; ISSN: 1389-2010

PB Bentham Science Publishers Ltd.

DT Journal; General Review

LA English

AB A ***review*** with 150 refs. Nonviral gene therapy has significant clin. potential, yet its therapeutic utility has been hindered by low transfection efficiency due to a combination of extracellular and intracellular barriers. Recent developments in formulation and delivery methodol. have allowed a no. of advances toward high efficiency gene delivery to various cell types and organs. In particular, the extracellular and intracellular pharmacokinetics of plasmid DNA trafficking are better understood in a no. of cell systems. Using cationic lipid or ***polymers*** (often with receptor targeting), more than 105 plasmids can be delivered to a single cell. ***Endosomolytic*** agents promote ***endosome*** disruption, and include: weak bases, proton-sponge ***polymers*** , fusogenic peptides, viral particles, and photosensitizing compds. Both classical and nonclassical nuclear localization signal (NLS) peptides have also been tested for enhancement of the probability of nuclear import events, a major rate-limiting step in DNA delivery to nondividing cells. For example, the M9 sequence from heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) protein, a non-classical NLS, has been found to increase gene expression level by more than 10 to 150-fold in a variety of cell types. This ***review*** will conc. on the current understandings of the basic mechanisms of nonviral gene delivery and new approaches in the field.

RE.CNT 150

L16 ANSWER 4 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001161276 EMBASE
TI Cationic ***p lymers*** f r gene delivery: Designs for overcoming barriers to systemic administration.
AU Hwang S.J.; Davis M.E.
CS S.J. Hwang, Insert Therapeutics Inc, 2585 Nina St, Pasedena, CA 91107, United States. shwang@insertt.com
SO Current Opinion in Molecular Therapeutics, (2001) 3/2 (183-191).
Refs: 71
ISSN: 1464-8431 CODEN: CUOTFO
CY United Kingdom
DT Journal; Article
FS 037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB Cationic, ***polymer*** -based delivery systems have faced limitations in the systemic delivery of therapeutic gene drugs due to difficulties in formulation, in vivo stabilization, toxicity and low transfection efficiencies. Strategies for overcoming some of these barriers have utilized knowledge gained from the fields of colloidal stabilization and protein trafficking. This ***review*** highlights recent efforts in polycation preparations that include the development of new ***polymers*** for gene delivery, the modification of traditional polycations with hydrophilic ***polymers*** for salt and serum stability and the addition of bioactive functionalities to ***polymers*** for enhanced intracellular trafficking. These studies have resulted in ***polymer*** /DNA composites with increased stability and delivery efficiencies.

L16 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 2001:670721 CAPLUS
TI Bioinspired ***polymers*** that control intracellular drug delivery
AU Hoffman, Allan S.; Stayton, Patrick S.; Press, Oliver; Murthy, Niren; Lackey, Chantal A.; Cheung, Charles; Black, Fiona; Campbell, Jean; Fausto, Nelson; Kyriakides, Themis R.; Bornstein, Paul
CS Department of Bioengineering, University of Washington, Seattle, WA, 98195, USA
SO Biotechnol. Bioprocess Eng. (2001), 6(4), 205-212
CODEN: BBEIAU; ISSN: 1226-8372
PB Korean Society for Biotechnology and Bioengineering
DT Journal
LA English
AB One of the important characteristics of biol. systems is their ability to change important properties in response to small environmental signals. The mol. mechanisms that biol. mols. utilize to sense and respond provide interesting models for the development of "smart" ***polymeric*** biomaterials with biomimetic properties. An important example of this is the protein coat of viruses, which contains peptide units that facilitate the trafficking of the virus int the cell via endocytosis, then out of the ***endos me*** int the cytoplasm, and from there into the nucleus. We hav designed a family of synthetic ***polymers*** whose compns. have be n designed t mimic specific peptides n viral coats that

facilitate endosomal escape. Our biomimetic ***polymers*** are responsive to the lowered pH within end s mes, leading to disruption of the endosomal membrane and release f important biomol. drugs such as DNA, RNA, peptides and proteins to the cytoplasm before they are trafficked to lysosomes and degraded by lysos mal enzymes. In this article, we ***review*** our work n the design, synthesis and action of such smart, pH-sensitive ***polymers*** .

facilitate endosomal escape. Our biomimetic ***polymers*** are responsive to the lowered pH within end somes, leading to disruption of the endosomal membran and release of important biomol. drugs such as DNA, RNA, peptides and proteins to the cytoplasm bef re they are trafficked to lysosomes and degraded by lysos mal enzymes. In this article, we ***review*** our work n the design, synthesis and action of such smart, pH-sensitive ***polymers*** .

(FILE 'HOME' ENTERED AT 14:30:31 ON 14 SEP 2001)

FILE 'MEDLINE, CANCERLIT, EMBASE, CAPLUS, BIOTECHDS, BIOSIS' ENTERED AT 14:31:29 ON 14 SEP 2001

L1 1481 S PH SENSITIVE AND (POLYMER OR NANOPARTICLE OR MICROSPHERE OR E
L2 126573 S ENDOSOME OR LYTIS OR LYSIS OR ENDOSOMOLYTIC
L3 20 S L2 AND 1L
L4 15 DUP REM L3 (5 DUPLICATES REMOVED)
L5 2745741 S DNA OR NUCLEIC OR PLASMID
L6 4006 S ORTHO AND ESTER
L7 25323 S HYDRAZONE OR ACETONYL
L8 29324 S L6 OR L7
L9 4 S L8 AND L1
L10 2 DUP REM L9 (2 DUPLICATES REMOVED)
L11 310295 S POLYESTER# OR POLYCARBO? OR POLYDISULFI?
L12 51 S L11 AND L1
L13 42 DUP REM L12 (9 DUPLICATES REMOVED)
L14 1 S L13 AND L5
L15 56 S L8 AND L2
L16 41 DUP REM L15 (15 DUPLICATES REMOVED)
L17 1 S L16 AND L5
L18 2 S L16 AND ENDOSO?
L19 2 S L16 AND ENDOCYT?
L20 155 S L11 AND L2
L21 11 S L20 AND (ENDOSO? OR ENDOCYTO?)
L22 6 DUP REM L21 (5 DUPLICATES REMOVED)

L10 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
AN 90319438 EMBASE
DN 1990319438
TI Release of insulin from ***pH*** - ***sensitive*** poly(***ortho*** esters).
AU Heller J.; Chang A.C.; Rodd G.; Grodsky G.M.
CS Controlled Release and, Biomedical Polymers Program, SRI International,Menlo Park, CA 94025, United States
SO Journal of Controlled Release, (1990) 13/2-3 (295-302).
AB The principal objective of this work is the development of a bioerodible insulin delivery device that will release insulin in response to the concentration of external glucose where release of insulin is modulated by pH changes resulting from a glucose-glucose oxidase reaction. A major component of such a delivery system is a bioerodible ***polymer*** than can reversibly change erosion rates in response to very small changes in the surrounding pH. We hav prepared such a ***polymer*** by incorporating tertiary amine gr ups into a linear poly(***ortho*** ***ester***). When insulin is incorp rated into this ***polymer***

Nguyen, Dave
T : STIC-ILL
Subject: reference request 09/553552

Please have the following references sent to Dave Nguyen, 12B15:

L6 ANSWER 11 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999032882 EMBASE
TI Gene transfer with synthetic virus-like particles via the integrin-mediated endocytosis pathway.
AU Erbacher P.; Remy J.-S.; Behr J.-P.
CS J.-P. Behr, UMR 7514 CNRS, Faculte de Pharmacie, Universite Louis Pasteur Strasbourg, BP 24, F-67401 Illkirch, France
SO Gene Therapy, (1999) 6/1 (138-145).
Refs: 64
ISSN: 0969-7128 CODEN: GETHEC
CY United Kingdom
DT Journal; Article
FS 029 Clinical Biochemistry
LA English

L6 ANSWER 10 OF 15 MEDLINE DUPLICATE 4
AN 2000083589 MEDLINE
DN 20083589 PubMed ID: 10617299
TI Pharmaceutical and biological properties of poly(amino acid)/DNA polyplexes.
AU Lucas P; Milroy D A; Thomas B J; Moss S H; Pouton C W
CS Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, UK.
SO JOURNAL OF DRUG TARGETING, (1999) 7 (2) 143-56.
Journal code: B3S; 9312476. ISSN: 1061-186X.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English

L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1999:625714 CAPLUS
DN 132:26739
TI Poly(amidoamine)s as potential endosomolytic polymers: evaluation in vitro and body distribution in normal and tumor-bearing animals
AU Richardson, S.; Ferruti, P.; Duncan, R.
CS Centre for Polymer Therapeutics, The School of Pharmacy, University of London, London, WC1N 1AX, UK
SO J. Drug Targeting (1999), 6(6), 391-404
CODEN: JDTAEH; ISSN: 1061-186X
PB Harwood Academic Publishers
DT Journal
LA English

L16 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 1997:349973 CAPLUS
DN 127:12866
TI The proton sponge: a trick the viruses did not exploit

AU Demeneix, Barbara A.; Behr, Jean Paul
CS Unite de Recherche Associee, Laboratoire de Physiologie Generale et Comparee, Museum National d'Histoire Naturelle, Paris, 75231, Fr.
SO Artif. Self-Assem. Syst. Gene Delivery, Two Conf. (1996), Meeting Date 1995, 146-151. Editor(s): Felgner, Philip L. Publisher: American Chemical Society, Washington, D. C.
CODEN: 64KHA5
DT Conference; General Review

L16 ANSWER 21 OF 27 MEDLINE DUPLICATE 5
AN 1998257905 MEDLINE
DN 98257905 PubMed ID: 9595549
TI Cationic lipids, phosphatidylethanolamine and the intracellular delivery of ***polymeric*** , nucleic acid-based drugs (***review***).
AU Hope M J; Mui B; Ansell S; Ahkong Q F
CS Inex Pharmaceuticals Corporation, Burnaby, B.C., Canada.
SO MOLECULAR MEMBRANE BIOLOGY, (1998 Jan-Mar) 15 (1) 1-14. Ref: 82
Journal code: BTQ; 9430797. ISSN: 0968-7688.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

L16 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
AN 1999:374469 CAPLUS
DN 131:174881
TI Peptide-based gene delivery
AU Mahato, Ram I.; Monera, Oscar D.; Smith, Louis C.; Rolland, Alain
CS Copernicus Therapeutics Inc, Cleveland, OH, 44106-3052, USA
SO Curr. Opin. Mol. Ther. (1999), 1(2), 226-243
CODEN: CUOTFO; ISSN: 1464-8431
PB Current Drugs Ltd.
DT Journal; General Review
LA English

L16 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1
AN 2001:240751 CAPLUS
DN 135:55312
TI Nonviral gene therapy and its delivery systems
AU Ma, Haiching; Diamond, Scott L.
CS Institute for Medicine and Engineering, Department of Chemical Engineering, 1024 Vagelos Research Laboratories, University of Pennsylvania, Philadelphia, PA, 19104, USA
SO Curr. Pharm. Biotechnol. (2001), 2(1), 1-17
CODEN: CPBUBP; ISSN: 1389-2010
PB Bentham Science Publishers Ltd.
DT Journal; General Review

L16 ANSWER 4 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001161276 EMBASE
TI Cationic ***polymers* for gene delivery: Designs for vercoming barriers to systemic administration.**
AU Hwang S.J.; Davis M.E.
CS S.J. Hwang, Insert Therapeutics Inc, 2585 Nina St, Pasedena, CA 91107,

United States. shwang@insertt.com
SO Current Opinion in Molecular Th rapeutics, (2001) 3/2 (183-191).
Refs: 71
ISSN: 1464-8431 CODEN: CUOTFO
CY United Kingdom
DT Journal; Article
FS 037 Drug Literature Index

L22 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1994:200306 CAPLUS
DN 120:200306
TI Study of the mechanism of interaction of poly(.epsilon.-caprolactone) nanocapsules with the cornea by confocal laser scanning microscopy
AU Calvo, Pilar; Thomas, Charles; Alonso, Maria J.; Vila-Jato, Jose L.; Robinson, Joseph R.
CS Lab. Farm. Galenica, Fac. Farm., Santiago de Compostela, 15706, Spain
SO Int. J. Pharm. (1994), 103(3), 283-91
CODEN: IJPHDE; ISSN: 0378-5173
DT Journal
LA English

L13 ANSWER 23 OF 42 CAPLUS COPYRIGHT 2001 ACS
AN 1998:315264 CAPLUS
DN 129:4944
TI New ***pH*** ***sensitive*** network. Combination of an amphiphilic degradable ***polyester*** with a .beta.-cyclodextrin copolymer
AU Moine, Laurence; Cammas, Sandrine; Amiel, Catherine; Renard, Estelle; Sebille, Bernard; Guerin, Philippe
CS Laboratoire Recherche Polymeres, Universite Paris XII-Val de Marne, Thiais, F-94320, Fr.
SO Macromol. Symp. (1998), 130, 45-52
CODEN: MSYMEC; ISSN: 1022-1360
L13 ANSWER 30 OF 42 CAPLUS COPYRIGHT 2001 ACS
AN 1995:915135 CAPLUS
DN 123:350080
TI Pharmacokinetics of a Novel HIV-1 Protease Inhibitor Incorporated into Biodegradable or Enteric Nanoparticles following Intravenous and Oral Administration to Mice
AU Leroux, Jean-Christophe; Cozens, Robert; Roesel, Johan L.; Galli, Bruno; Kubel, Frank; Doelker, Eric; Gurny,Robert
CS School of Pharmacy, University of Geneva, Geneva, CH-1211, Switz.
SO J. Pharm. Sci. (1995), 84(12), 1387-91
CODEN: JPMSAE; ISSN: 0022-3549

L10 ANSWER 2 OF 2 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
AN 90319438 EMBASE
DN 1990319438
TI Release of insulin from ***pH*** - ***sensitive*** poly(***ortho*** esters).
AU Heller J.; Chang A.C.; Rodd G.; Grodsky G.M.
CS Controlled Release and, Bi medical Polym rs Pr gram, SRI International,Menlo Park, CA 94025, United States
SO Journal of Controlled Release, (1990) 13/2-3 (295-302).
AB The principal objective of this work is the development of a bioerodible

L16 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 2001:670721 CAPLUS
TI Bioinspired ***polymers*** that control intracellular drug delivery
AU Hoffman, Allan S.; Stayt n, Patrick S.; Press, Oliver; Murthy, Niren; Lackey, Chantal A.; Cheung, Charles; Black, Fiona; Campbell, Jean; Fausto, Nelson; Kyriakides, Themis R.; Bornstein, Paul
CS Department of Bioengineering, University of Washington, Seattle, WA, 98195, USA
SO Biotechnol. Bioprocess Eng. (2001), 6(4), 205-212
CODEN: BBEIAU; ISSN: 1226-8372
PB Korean Society for Biotechnology and Bioengineering
DT Journal
LA English

Dave Nguyen
AU 1633
CM1-12B15
305-2024

(FILE 'HOME' ENTERED AT 12:08:41 ON 14 SEP 2001)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, CAPLUS, EMBASE' ENTERED AT 12:08:56 ON 14 SEP 2001

L1 634712 S NANOPARTICLE OR NM
L2 6767 S ENDOSOMOLYTIC OR ENDOSOME
L3 328 S L1 AND L2
L4 1971616 S MONOMER OR POLYME?
L5 24 S L4 AND L3
L6 15 DUP REM L5 (9 DUPLICATES REMOVED)
L7 3697 S ORTHO AND ESTER
L8 892 S L7 AND L4
L9 0 S L8 AND L2
L10 124892 S SENSITIVE AND PH
L11 26 S L3 AND L10
L12 14 DUP REM L11 (12 DUPLICATES REMOVED)
L13 2 S ENDOSOMOLYTIC COMPOUND OR ENDOSOMOLYTIC POLYMER
L14 513 S L2 AND REVIEW
L15 34 S L14 AND L4
L16 27 DUP REM L15 (7 DUPLICATES REMOVED)

L6 ANSWER 11 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999032882 EMBASE
TI Gene transfer with synthetic virus-like particles via the integrin-mediated endocytosis pathway.
AU Erbacher P.; Remy J.-S.; Behr J.-P.
CS J.-P. Behr, UMR 7514 CNRS, Faculte de Pharmacie, Universite Louis Pasteur Strasbourg, BP 24, F-67401 Illkirch, France
SO Gene Therapy, (1999) 6/1 (138-145).
Refs: 64
ISSN: 0969-7128 CODEN: GETHEC
CY United Kingdom
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB The interaction between cationic DNA-containing particles and cell surface anionic proteoglycans is an efficient means of entering cultured cells. Therapeutic in vivo gene delivery levels, however, require binding to less ubiquitous molecules. In an effort to follow adenovirus, thiol-derivatized polyethylenimine (PEI) was conjugated to the integrin-binding peptide CYGGRGDTP via a disulfide bridge. The most extensively conjugated derivative (5.5% of the PEI amine functions) showed physical properties of interest for systemic gene delivery. In the presence of excess PEI-RGD, plasmid DNA was condensed into a rather homogeneous population of 30-100 ***nm*** toroidal particles as by electron microscopy images in 150 mM salt. Their surface charge was close to neutrality as a consequence of the shielding effect of the prominent zwitterionic peptide residues. Transfection efficiency of integrin-expressing epithelial (HeLa) and fibroblast (MRC5) cells was increased by 10- to 100-fold as compared with PEI, even in serum. This large enhancement factor was lost when aspartic acid was replaced by glutamic acid in the targeted peptide sequence (RGD/RGE), confirming the involvement of integrins in transfection. PEI-RGD/DNA complexes thus share with adenovirus constitutive properties

such as size and a centrally protected DNA core, and 'early' properties, ie cell entry mediated by integrins and acid-triggered ***endosome*** escape.

L6 ANSWER 10 OF 15 MEDLINE DUPLICATE 4
AN 2000083589 MEDLINE
DN 20083589 PubMed ID: 10617299
TI Pharmaceutical and biological properties of poly(amino acid)/DNA polyplexes.
AU Lucas P; Milroy D A; Thomas B J; Moss S H; Pouton C W
CS Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, UK.
SO JOURNAL OF DRUG TARGETING, (1999) 7 (2) 143-56.
Journal code: B3S; 9312476. ISSN: 1061-186X.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200002
ED Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000202
AB Physicochemical properties of polyplexes formed between pRSVlacZ and poly(amino acid)s were investigated as a paradigm of more complex, synthetic virus-like, DNA delivery systems, that are of interest to many gene delivery laboratories. We observed the interaction between ***polymer*** and DNA using ethidium exclusion, and determined the size distributions and the zeta potentials of polyplexes. We correlated these properties with their fundamental interactions with cultured B16 murine melanoma cells, and the resulting efficiency of transfection. A variety of poly(amino acid)s each condensed DNA to produce particles with mean hydrodynamic diameters of approximately 100 ***nm*** (a typical span of a population was 80-120nm). Poly(amino acid) polyplexes were unstable in electrolyte solutions such as cell culture media. The apparent particle size increased in electrolyte, depending on the charge ratio, to diameters up to 700 ***nm*** . This was thought to be due to aggregation, since neutral particles were most sensitive. When the charge ratio (+/-) exceeded unity polyplexes had positive zeta potentials (which peaked at approximately +30 mV), bound non-specifically to cells, were internalised and in the presence of an ***endosomolytic*** agent were able to transfect cells. Though all cationic poly(amino acid)s investigated formed polyplexes with similar physical properties, their biological properties were significantly different. Polyplexes prepared with poly-L-ornithine were the most effective transfection agents, but poly(lys-co-ala, 1: 1) systems appeared to be inactive. This may reflect the differences in uncoupling of DNA and ***polymer*** , which is expected to be necessary for passage through the nuclear pore. Uncoupling of polycation and DNA was investigated by exposing the complexes to dextran sulphate. Release of DNA was detected by increased fluorescence at 600 ***nm*** in the presence of ethidium. Release of DNA was incomplete from polyplexes formed with high molecular weight polylysine. This may explain the lower levels of transfection observed with high molecular weight polylysine. The significance of these observations for design of advanced non-viral gene delivery systems is discussed.

still increased in efficacy when chloroquine was included.

L6 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2001 ACS
AN 1999:390393 CAPLUS
DN 131:40529
TI In situ formation of particulate complexes of polycations and nucleic acids for delivery to animal cells
IN Behr, Jean-Paul; Blessing, Thomas; Wagner, Ernst; Schuller, Susanne
PA Boehringer Ingelheim International GmbH, Germany; Universite Louis Pasteur de Strasbourg
SO PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

L6 ANSWER 8 OF 15 MEDLINE DUPLICATE 3
AN 2001030037 MEDLINE
DN 20450761 PubMed ID: 10995206
TI pH-sensitive cationic ***polymer*** gene delivery vehicle: N-Ac-poly(L-histidine)-graft-poly(L-lysine) comb shaped ***polymer*** .
AU Benns J M; Choi J S; Mahato R I; Park J S; Kim S W
CS Center for Controlled Chemical Delivery, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, Utah 84112, USA.
SO BIOCONJUGATE CHEMISTRY, (2000 Sep-Oct) 11 (5) 637-45.
Journal code: A1T. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001121
AB Advancing biotechnology spurs the development of new pharmaceutically engineered gene delivery vehicles. Poly(L-histidine) PLH has been shown to induce membrane fusion at endosomal pH values, whereas PLL has a well documented efficacy in polyplex formation. Therefore, N-Ac-poly(L-histidine)-graft-poly(L-lysine) PLH-g-PLL was synthesized by grafting poly(L-histidine) to poly(L-lysine) PLL . PLH-g-PLL formed polyplex particles by electrostatic interactions with plasmid DNA pDNA . The mean particle size of the polyplexes was in the range of 117 +/- 6 ***nm*** to 306 +/- 77 ***nm*** . PLH-g-PLL gene carrier demonstrated higher transfection efficacy in 293T cells than PLL at all equivalent weight ratios with pDNA. The inclusion of chloroquine as an ***endosomolytic*** agent enhanced transfection for both PLL and PLH-g-PLL gene carriers. PLH-g-PLL enhanced beta-galactosidase expression compared to PLL, but still increased in efficacy when chloroquine was included.

L6 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2001 ACS
AN 2001:404575 CAPLUS
DN 135:157526
TI Poly(Amidoamine)s as Potential Nonviral Vectors: Ability to Form Interpolyelectrolyte Complexes and to Mediate Transfection in Vitro
AU Richardson, Simon C. W.; Pattrick, Nicola G.; Man, Y. K. Stella; Ferruti, Paolo; Duncan, Ruth

CS Centre for Polymer Therapeutics Welsh School of Pharmacy, Cardiff University, Cardiff, CF10 3XF, UK
SO Biomacromolecules (2001), 2(3), 1023-1028
CODEN: BOMAF6; ISSN: 1525-7797
PB American Chemical Society
DT Journal
LA English
AB Poly(amidoamine)s (PAAs) are water-sol. ***polymers*** that display pH-dependent membrane activity. PAAs have the potential to act as a synthetic alternative to fusogenic peptides and thus promote endosomal escape. The purpose of this study was to investigate for the first time whether PAA have the ability to complex DNA, protect it from nuclease degrdn. and to promote transfection in vitro. PAAs ISA 1 (Mn 6900) and ISA 23 (Mn 10 500) and their 2-phenylethylamine contg. analogs ISA 4 and ISA 22 (Mn .apprx.8000) were studied. All PAAs retarded the electrophoretic mobility of .lambda. Hind III DNA demonstrating interpolyelectrolyte complex (IPEC) formation and toroids of 80-150 ***nm*** in diam. (10:1 ***polymer*** excess) were visible using TEM. DNase II inhibition was obsd. At a ***polymer*** :DNA ratio of 10:1, this was ISA 1(89.6 .+-. 6.1%), ISA 4 (92.2 .+-. 11.2%), ISA 22 (69.4 .+-. 3.7%), and ISA 23 (58.0 .+-. 10.0%). PAAs demonstrated the ability to mediate pSV .beta.-galactosidase transfection of HepG2 cells. At a vector:DNA mass ratio of 5:1, ISA 23 showed equiv. transfection ability compared with polyethylenimine and LipofectIN and was more effective than LipofectACE. These properties suggest that PAAs warrant further development as

L6 ANSWER 1 OF 15 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001053181 EMBASE
TI ***Polymer*** -based gene delivery with low cytotoxicity by a unique balance of side-chain termini.
AU Putnam D.; Gentry C.A.; Pack D.W.; Langer R.
CS R. Langer, Department of Chemical Engineering, MA Institute of Technology, Cambridge, MA 02139, United States. rlanger@mit.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (30 Jan 2001) 98/3 (1200-1205).
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB Protein expression after delivery of plasmid DNA to the cell nucleus depends on the processes of transcription and translation. Cytotoxic gene-delivery systems may compromise these processes and limit protein expression. This situation is perhaps most prevalent in current nonviral polycationic gene-delivery systems in which the polycationic nature of the delivery system can lead to cytotoxicity. To approach the problem of creating nontoxic but effective gene-delivery systems, we hypothesized that by optimizing the balance between ***polymer*** cationic density with endosomal escape moieties, effective gene transfer with low cytotoxicity could be created. As a model system, we synthesized a series of ***polymers*** whose side-chain termini varied with respect to the balance of cationic centers and endosomal escape moieties. Specifically, by ***polymer*** -analogous amidation we conjugated imidazole groups to the .epsilon.-amines of polylysine in varying mole ratios (73.5 mol % imidazole, 82.5 mol % imidazole, and 86.5 mol % imidazole). The primary

.epsilon.-amine terminus of polylysine served as a model for the cationic centers, whereas the imidazole groups served as a model for the endosomal escape moieties. These ***polymers*** condensed plasmid DNA into nanostructures <150 ***nm*** and possessed little cytotoxicity in vitro. Transfection efficiency, as measured by luciferase protein expression, increased with increasing imidazole content of the ***polymers*** in a nonlinear relationship. The ***polymer*** with the highest imidazole content (86.5 mol %) mediated the highest protein expression, with levels equal to those mediated by polyethylenimine, but with little to no cytotoxicity.

L13 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1999:625714 CAPLUS
DN 132:26739
TI Poly(amidoamine)s as potential endosomolytic polymers: evaluation in vitro and body distribution in normal and tumor-bearing animals
AU Richardson, S.; Ferruti, P.; Duncan, R.
CS Centre for Polymer Therapeutics, The School of Pharmacy, University of London, London, WC1N 1AX, UK
SO J. Drug Targeting (1999), 6(6), 391-404
CODEN: JDTAEH; ISSN: 1061-186X
PB Harwood Academic Publishers
DT Journal
LA English
AB Fusogenic peptides derived from viral coat proteins cause perturbation of the endosomal membrane and are often used to improve the transfection efficiency of non-viral vectors in vitro. However, fusogenic peptides have limited potential for use in vivo due to their inherent immunogenicity. Totally synthetic polymers that are endosomolytic should circumvent this problem and could be useful as components of non-viral delivery systems as long as they do not immediately localize in the liver after i.v. injection. Linear poly(amidoamine) polymers (PAAs) having amido- and tertiary amino-groups along the main polymer undergo pH-dependent conformational change and thus provide an ideal opportunity for design of polymers that display membrane activity at low pH. Here we describe four PAAs, ISA 1 (Mn = 6900 Da) and ISA 23 (Mn = 10,500 Da) and their analogs ISA 4 and ISA 22 (Mn approx. 8000 Da) contg. approx. 1 mol% 2-p-hydroxyphenylethylamine to allow radioiodination and thus monitoring of their biodistribution. In vitro cytotoxicity was assessed by MTT assay after incubation of PAAs with B16F10 and Mewo cell lines. The IC50 values obsd. for all PAAs were >2 mg/mL in comparison with poly(L-lysine) which displayed an IC50 in the range 0.01 - 0.1 mg/mL. At pH 7.4 none of the PAAs studied was hemolytic at 1 h at concns. below 3 mg/mL. PAAs were subsequently incubated with rat red blood cells for 24h (1 mg/mL) at different pHs. In contrast to poly(L-lysine) which was hemolytic at pH 7.4, 6.5 and 5.5, none of the PAAs was lytic at pH 7.4, but they became membrane active at lower pH (.apprx.45% for ISA 4, 50% for ISA 22 and 90% for ISA 23). These observations were substantiated by SEM and confirm the pH-dependence of membrane activity. After i.v. injection to rats 125I-labeled ISA 4 was immediately taken up by the liver (>80% recovered dose at 1 h) whereas 125I-labeled ISA 22 was not (liver uptake was <10% recovered dose at 5h). Furthermore, biodistribution studies in mice bearing s.c. B16F10 melanoma showed that 125I-labeled ISA 22 was still accumulating in tumor tissue after 5 h (2.5% dose/g). PAAs have potential as endosomolytic agents and quantitation of the endosome to cytoplasm transfer is warranted after i.v. administration.

L16 ANSWER 24 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 1997:349973 CAPLUS
DN 127:12866
TI The proton sponge: a trick the viruses did not exploit
AU Demeneix, Barbara A.; Behr, Jean Paul
CS Unite de Recherche Associee, Laboratoire de Physiologie Generale et Comparee, Museum National d'Histoire Naturelle, Paris, 75231, Fr.
SO Artif. Self-Assem. Syst. Gene Delivery, Two Conf. (1996), Meeting Date 1995, 146-151. Editor(s): Felgner, Philip L. Publisher: American Chemical Society, Washington, D. C.
CODEN: 64KHA5
DT Conference; General Review
LA English
AB A ***review*** with 18 refs. Several non-permanent polycations possessing substantial buffering capacity below physiol. pH, such as lipopolyamines and polyethylenimines, are efficient transfection agents per se, i.e. without the addn. of lysosomotropic bases, or cell targeting or membrane disruption agents. These vectors have been shown to deliver genes as well as oligonucleotides both in vitro and in vivo. Our hypothesis is that their efficiency relies on extensive ***endosome*** swelling and rupture that provides an escape mechanism for the polycation/DNA particles.

L16 ANSWER 21 OF 27 MEDLINE DUPLICATE 5
AN 1998257905 MEDLINE
DN 98257905 PubMed ID: 9595549
TI Cationic lipids, phosphatidylethanolamine and the intracellular delivery of ***polymeric*** , nucleic acid-based drugs (***review***).
AU Hope M J; Mui B; Ansell S; Ahkong Q F
CS Inex Pharmaceuticals Corporation, Burnaby, B.C., Canada.
SO MOLECULAR MEMBRANE BIOLOGY, (1998 Jan-Mar) 15 (1) 1-14. Ref: 82
Journal code: BTQ; 9430797. ISSN: 0968-7688.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199807
ED Entered STN: 19980731
Last Updated on STN: 19980731
Entered Medline: 19980723
AB ***Polymeric*** , nucleic acid drugs must be protected from endogenous nucleases and delivered to target cell nuclei in order to maximize their activity. Constructs expressing therapeutic genes, antisense oligonucleotides and ribozymes can be delivered into cells by viral vectors, but concerns over safety and clinical utility have led to research into the development of alternative, non-viral delivery systems. Antisense and ribozyme drug development has focused upon modifications to the natural oligonucleotide chemistry which make the molecules resistant to nuclease degradation. These novel oligonucleotides cannot be generated by transgenes and must be administered in similar fashion to conventional drugs. However, oligonucleotides cannot cross membranes by passive diffusion and intracellular delivery for these drugs is very inefficient.

Here we ***review*** the recent advances in forming lipid-DNA particles designed to mimic viral delivery of DNA. Most evidence now supports the hypothesis that lipid-DNA drugs enter target cells by endocytosis and disrupt the endosomal membrane, releasing nucleic acid into the cytoplasm. The mechanisms of particle formation and ***endosome*** disruption are not well understood. Cationic lipids are employed to provide an electrostatic interaction between the lipid carrier and polyanionic nucleic acids, and they are critical for efficient packaging of the drugs into a form suitable for systemic administration. However, their role in ***endosome*** disruption and other aspects of successful delivery leading to gene expression or inhibition of mRNA translation are less clear. We discuss the propensity of lipid-nucleic acid particles to undergo lipid mixing and fusion with adjacent membranes, and how phosphatidylethanolamine and other lipids may act as factors capable of disrupting bilayer structure and the endosomal pathway. Finally, we consider the challenges that remain in bringing nucleic acid

L16 ANSWER 17 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 1998:507894 CAPLUS
DN 129:254215
TI Theory and practice of using polycationic amphiphiles and ***polymers*** for in vitro and in vivo gene transfer
AU Demeneix, B. A.; Goula, D.; Benoist, C.; Remy, J. S.; Behr, J. P.
CS Laboratoire de Physiologie Generale et Comparee, U.R.A.90 CNRS, Museum National d'Histoire Naturelle, Paris, F-75231, Fr.
SO NATO ASI Ser., Ser. H (1998), 105(Gene Therapy), 195-204
CODEN: NASBE4; ISSN: 1010-8793
PB Springer-Verlag
DT Journal; General Review
LA English
AB A ***review*** with 28 refs. The mechanisms underlying the actions of polycationic (as opposed to monocationic) gene transfer vectors is described. Two main types of vectors are examd., polycationic amphiphiles such as DOGS (Transfectam) and Lipofectamine on the one hand and cationic ***polymers*** such as polyethyleneimine on the other hand. The gene transfer performances of these mols. is a function of their DNA condensing capacity, their interactions with anionic proteoglycans of the cell membrane and their capacity to induce ***endosome*** swelling and rupture. The importance of taking into account the overall charge ratio of complexes when carrying out in vitro or in vivo gene transfer is emphasi

L16 ANSWER 14 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
AN 1999:374469 CAPLUS
DN 131:174881
TI Peptide-based gene delivery
AU Mahato, Ram I.; Monera, Oscar D.; Smith, Louis C.; Rolland, Alain
CS Copernicus Therapeutics Inc, Cleveland, OH, 44106-3052, USA
SO Curr. Opin. Mol. Ther. (1999), 1(2), 226-243
CODEN: CUOTFO; ISSN: 1464-8431
PB Current Drugs Ltd.
DT Journal; General Review
LA English
AB A ***review*** with 147 refs. To achieve effective plasmid-based gene therapy, the control of cellular access and uptake, intracellular trafficking and nuclear retention of plasmids must be achieved.

Inefficient endosomal release, cytoplasmic transport and nuclear entry of plasmids are amongst some of the key limiting factors in the use of plasmids for effective gene therapy. A no. of non-viral gene delivery systems have been designed to overcome these limiting factors. The most common approach to protect and control plasmid distribution is to complex plasmids with cationic lipids or ***polymers*** through electrostatic interactions. Endosomal release of plasmids can be achieved, for instance, by using pH-sensitive lipids, inactivated viral particles, ***endosomolytic*** peptides and ***polymers*** . Among the least explored gene delivery systems are those that consist mainly of synthetic, short peptides. Peptides can be incorporated into multi-component gene delivery complexes for specific purposes, such as for DNA condensation, cell-specific targeting, endosomolysis or nuclear transport. The aims of this ***review*** are to: (i) explore the conceptual and exptl. aspects of peptide-DNA interactions; (ii) critically assess the possible use of peptides for efficient gene transfer; and (iii) present an overview on the use of peptides to enhance the effectiveness of other gene delivery systems. On balance, peptide-based gene delivery systems appear to have a significant potential as com. viable gene delivery products.

R

L16 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 1

AN 2001:240751 CAPLUS

DN 135:55312

TI Nonviral gene therapy and its delivery systems

AU Ma, Haiching; Diamond, Scott L.

CS Institute for Medicine and Engineering, Department of Chemical Engineering, 1024 Vagelos Research Laboratories, University of Pennsylvania, Philadelphia, PA, 19104, USA

SO Curr. Pharm. Biotechnol. (2001), 2(1), 1-17
CODEN: CPBUBP; ISSN: 1389-2010

PB Bentham Science Publishers Ltd.

DT Journal; General Review

LA English

AB A ***review*** with 150 refs. Nonviral gene therapy has significant clin. potential, yet its therapeutic utility has been hindered by low transfection efficiency due to a combination of extracellular and intracellular barriers. Recent developments in formulation and delivery methodol. have allowed a no. of advances toward high efficiency gene delivery to various cell types and organs. In particular, the extracellular and intracellular pharmacokinetics of plasmid DNA trafficking are better understood in a no. of cell systems. Using cationic lipid or ***polymers*** (often with receptor targeting), more than 105 plasmids can be delivered to a single cell. ***Endosomolytic*** agents promote ***endosome*** disruption, and include: weak bases, proton-sponge ***polymers*** , fusogenic peptides, viral particles, and photosensitizing compds. Both classical and nonclassical nuclear localization signal (NLS) peptides have also been tested for enhancement of the probability of nuclear import events, a major rate-limiting step in DNA delivery to nondividing cells. For example, the M9 sequence from heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) protein, a non-classical NLS, has been found to increase gene expression level by more than 10 to 150-fold in a variety of cell types. This ***review*** will conc. on the current understandings of the basic mechanisms of nonviral gene delivery and new approaches in the field.

RE.CNT 150

L16 ANSWER 4 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2001161276 EMBASE
TI Cationic ***polymers*** for gene delivery: Designs for overcoming barriers to systemic administrati n.
AU Hwang S.J.; Davis M.E.
CS S.J. Hwang, Insert Therapeutics Inc, 2585 Nina St, Pasedena, CA 91107, United States. shwang@insertt.com
SO Current Opinion in Molecular Therapeutics, (2001) 3/2 (183-191).
Refs: 71
ISSN: 1464-8431 CODEN: CUOTFO
CY United Kingdom
DT Journal; Article
FS 037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB Cationic, ***polymer*** -based delivery systems have faced limitations in the systemic delivery of therapeutic gene drugs due to difficulties in formulation, in vivo stabilization, toxicity and low transfection efficiencies. Strategies for overcoming some of these barriers have utilized knowledge gained from the fields of colloidal stabilization and protein trafficking. This ***review*** highlights recent efforts in polycation preparations that include the development of new ***polymers*** for gene delivery, the modification of traditional polycations with hydrophilic ***polymers*** for salt and serum stability and the addition of bioactive functionalities to ***polymers*** for enhanced intracellular trafficking. These studies have resulted in ***polymer*** /DNA composites with increased stability and delivery efficiencies.

L16 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2001 ACS
AN 2001:670721 CAPLUS
TI Bioinspired ***polymers*** that control intracellular drug delivery
AU Hoffman, Allan S.; Stayton, Patrick S.; Press, Oliver; Murthy, Niren; Lackey, Chantal A.; Cheung, Charles; Black, Fiona; Campbell, Jean; Fausto, Nelson; Kyriakides, Themis R.; Bornstein, Paul
CS Department of Bioengineering, University of Washington, Seattle, WA, 98195, USA
SO Biotechnol. Bioprocess Eng. (2001), 6(4), 205-212
CODEN: BBEIAU; ISSN: 1226-8372
PB Korean Society for Biotechnology and Bioengineering
DT Journal
LA English
AB One of the important characteristics of biol. systems is their ability to change important properties in response to small environmental signals. The mol. mechanisms that biol. mols. utilize to sense and respond provide interesting models for the development of "smart" ***polymeric*** biomaterials with biomimetic properties. An important example of this is the protein coat of viruses, which contains peptide units that facilitate the trafficking of the virus int the cell via endocytosis, then out of the ***endosome*** into the cytoplasm, and from there into the nucleus. We have designed a family f synthetic ***polymers*** whose compns. have been designed to mimic sp cific peptides on viral coats that

and thin disks subjected t well defined pH pulses, th ***polymer*** responds rapidly and reversibly t thes pH pulses. Current eff rts involve preparation of gluc se sensitiv devices by surr unding the insulin-containing ***polymer*** with a microp rous hydrogel-containing imm bilized glucose xidase. When glucose diffuses into the device, gluconic acid pr duced within the hydr gel will decrease the ambient pH thus triggering release of insulin. The hydrogel is microporous to permit rapid release of insulin from the ***polymer*** to the surrounding environment.

L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2001 ACS
AN 2000:881174 CAPLUS
DN 134:61521
TI Compositions and methods for delivery of drugs and ***nucleic*** acids using ***pH*** ***sensitive*** molecules
IN Wolff, Jon A.
PA Mirus Corporation, USA
SO PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000075164	A1	20001214	WO 2000-US15651	20000607
W: JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1102785	A1	20010530	EP 2000-939634	20000607
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI US 1999-137859 P 19990607
US 1999-167836 P 19991129
US 1999-172809 P 19991221
WO 2000-US15651 W 20000607

AB A system relating to the delivery of desired compds. (e.g., drugs and ***nucleic*** acids) into cells using ***pH*** - ***sensitive*** delivery systems is presented. The system provides compns. and methods for the delivery and release of a compd. to a cell. Transfection of Hela cells with histone H1 and the membrane active peptide melittin, dimethylmaleic-modified melittin or succinic anhydride-modified melittin was carried out. The 2,3-dimethylmaleic modification of melittin allowed the peptide to complex with the cationic protein histone H1 and then cleave to release and reactivate in the lowered pH encountered by the complex in the cellular endosomal compartment. This caused a significant increase in luciferase expression over either unmodified melittin peptide or melittin peptide modified with succinic anhydride which allows complexing with histone H1 but does not cleave in lowered pH.

RE.CNT 4
RE
(1) Curiel; US 5547932 A 1996 CAPLUS
(2) L R S Diagnostics Inc; WO 9323433 A1 1993 CAPLUS
(3) Mirus Corporation; WO 9829541 A1 1998 CAPLUS
(4) Mirus Corporation; WO 9852961 A1 1998 CAPLUS

L13 ANSWER 34 OF 42 MEDLINE DUPLICATE 4
AN 93284959 MEDLINE
DN 93284959 PubMed ID: 8508694
TI Olestra, a nondigestible, nonabs rbable fat. Effects n gastrointestinal and colonic transit.
AU Aggarwal A M; Camilleri M; Phillips S F; Schlagheck T G; Brown M L; Thomforde G M
CS Gastroenterology Research Unit, Mayo Clinic, Rochester, Minnesota 55905.
NC DK32121 (NIDDK)
DK34988 (NIDDK)
RR00585 (NCRR)
SO DIGESTIVE DISEASES AND SCIENCES, (1993 Jun) 38 (6) 1009-14.
Journal code: EAD; 7902782. ISSN: 0163-2116.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals

L13 ANSWER 30 OF 42 CAPLUS COPYRIGHT 2001 ACS
AN 1995:915135 CAPLUS
DN 123:350080
TI Pharmacokinetics of a Novel HIV-1 Protease Inhibitor Incorporated into Biodegradable or Enteric Nanoparticles following Intravenous and Oral Administration to Mice
AU Leroux, Jean-Christophe; Cozens, Robert; Roesel, Johan L.; Galli, Bruno; Kubel, Frank; Doelker, Eric; Gurny,Robert
CS School of Pharmacy, University of Geneva, Geneva, CH-1211, Switz.
SO J. Pharm. Sci. (1995), 84(12), 1387-91
CODEN: JPMSAE; ISSN: 0022-3549
DT LA English
AB CGP 57813 is a peptidomimetic inhibitor of human immunodeficiency virus type 1 (HIV-1) protease. This lipophilic compd. was successfully entrapped into poly(D,L-lactic acid) (PLA) and ***pH*** ***sensitive*** methacrylic acid copolymers nanoparticles. The i.v. administration to mice of PLA nanoparticles loaded with CGP 57813 resulted in a 2-fold increase of the area under the plasma concn.-time curve, compared to a control soln. An increase in the elimination half-life (from 13 to 61 min) and in the apparent vol. of distribution (1.7-3.6 L/kg) was obsd. for the ***nanoparticle*** incorporated compd. vs control soln. Following oral administration, only nanoparticles made of the methacrylic acid copolymer sol. at low pH provided sufficient plasma levels of CGP 57813. In vitro, these nanoparticles dissolved completely within 5 min at pH 5.6. PLA nanoparticles, which are insol. in the gastrointestinal tract, did not provide significant plasma concns. of CGP 57813. From these observations, one can conclude that the passage of intact PLA nanoparticles across the gastrointestinal mucosa appears to be very low.

L13 ANSWER 24 OF 42 CAPLUS COPYRIGHT 2001 ACS
AN 1997:226810 CAPLUS
DN 126:216686
TI Novel compositions and devices for controlled release of active

ingredients
IN Batich, Christopher D.; Cohen, Marc S.; Foster, Kirk; Toreki, William, Iii
PA Caphco, Inc., USA
SO PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9704819	A1	19970213	WO 1996-US12226	19960725
W: CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5788687	A	19980804	US 1995-509120	19950731
PRAI US 1995-509120		19950731		
US 1994-189854		19940201		
US 1995-382315		19950201		

AB A method for the controlled release of a biol. active agent wherein the agent is released from a hydrophobic, ***pH*** - ***sensitive*** ***polymer*** ***matrix*** is disclosed and claimed. In one embodiment, the ***polymer*** ***matrix*** swells when the environment reaches pH 8.5, releasing the active agent. A ***polymer*** of hydrophobic and weakly acidic comonomers is disclosed for use in the controlled release system. In another embodiment, weakly basic comonomers are used and the active agent is released as the pH drops. Further disclosed is a specific embodiment in which the controlled release system may be used. The ***pH*** - ***sensitive*** ***polymer*** is coated onto a latex catheter used in ureteral catheterization. A common problem with catheterized patients is the infection fo the urinary tract with urease-producing bacteria. In addn. to the irritation caused by the presence of the bacteria, urease produced by these bacteria degrade urea in the urine, forming carbon dioxide and ammonia. The ammonia causes an increase in the pH of the urine. Minerals in the urine begin to ppt. at this high pH, forming encrustations which complicate the functioning of the catheter. A ureteral catheter coated with a ***pH*** - ***sensitive*** ***polymer*** having an antibiotic or urease inhibitor trapped within its ***matrix*** releases the active agent when exposed to the high pH urine as the ***polymer*** gel swells. Such release can be made slow enough so that the drug remains at significant levels for a clin. useful period of time. Other uses for the methods and devices of this invention include use in gastrointestinal tubes, respiratory trap lines and ventilation tubes, dye releasing ***pH*** - ***sensitive*** sutures, active agent release from contact lenses, penile implants, heart pacemakers, neural shunts, food wraps, and clean room walls.

different pH buffers were also studied.

L13 ANSWER 23 OF 42 CAPLUS COPYRIGHT 2001 ACS
AN 1998:315264 CAPLUS
DN 129:4944
TI New ***pH*** ***sensitive*** network. Combination of an amphiphilic degradable ***polyester*** with a .beta.-cyclodextrin copolymer
AU Moine, Laurence; Cammas, Sandrine; Amiel, Catherin ; Renard, Estelle; Sebille, Bernard; Guerin, Philippe

CS Laboratoire Recherche Polymeres, Universite Paris XII-Val de Marne, Thiais, F-94320, Fr.
SO Macromol. Symp. (1998), 130, 45-52
CODEN: MSYMEC; ISSN: 1022-1360
PB Huethig & Wepf Verlag
DT Journal
LA English
AB A novel hydrophobic monomer, adamantylethyl malolactonate, has been synthesized and copolymd. with benzyl malolactonate by anionic ring-opening polymn. The ratio of adamantyl monomer varied from 0-100 mol%. Deprotection of benzyl groups leads to a water sol. copolyester with carboxylic acid lateral functions which give a polyelectrolyte character to the corresponding polymers. The mixt. of a copolyester contg. 10% of adamantyl groups and a .beta.-cyclodextrin/epichlorohydrin copolymer in aq. soln. leads to a new pH-dependant assocg. system. The soln. behavior of this system was studied by viscosimetry as a function of pH, concn., and ratio of both copolymers. At the initial soln. pH (pH = 2), the copolyester adopts a coiled structure as a result of hydrophobic interactions between the pendant adamantyl groups. Consequently, no network formation is obsd. as shown by a very low viscosity. As the pH increase, the viscosity of the medium increases and reaches a max. at pH = 5. At this pH, the copolyester expands because of electrostatic repulsions between the carboxylate pendant functions. Consequently, the adamantyl groups are accessible and can be ***encapsulated*** into the .beta.-cyclodextrin cavities resulting in a significant increase of the viscosity.

L13 ANSWER 22 OF 42 CAPLUS COPYRIGHT 2001 ACS
AN 1998:527405 CAPLUS
TI ***pH*** - ***sensitive*** hydrogels based on chitosan and D,L-lactic acid.
AU Qu, Xin; Wirsen, Anders; Albertsson, Ann-Christine
CS Department Polymer Technology, Royal Institute Technology, Stockholm, S-100 44, Swed.
SO Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), PMSE-110 Publisher: American Chemical Society, Washington, D. C.
CODEN: 66KYA2
DT Conference; Meeting Abstract
LA English
AB Novel ***pH*** - ***sensitive*** hydrogels were synthesized by grafting D,L-lactic acid(LA) onto the amino groups in chitosan(CS) without catalyst. ***pH*** - ***Sensitive*** hydrogels were obtained which based on two different components: a natural ***polymer*** and a synthetic ***polymer*** . These ***polyester*** substituents provide the basis for hydrophobic interactions which contribute to the formation of hydrogels. The crystallizability of chitosan gradually decreased after grafting, since the PLA side chains substitute the -NH2 groups of chitosan randomly along the chain and destroy the regularity of packing between chitosan chains. Meanwhile, specific soln. content of the hydrogels was investigated as a function of the chitosan to PLA ratio, pH and salt concn. of the buffers. The structure change of hydrogels in different pH buffers were also studied.

L13 ANSWER 6 OF 42 CAPLUS COPYRIGHT 2001 ACS
AN 1999:34955 CAPLUS

DN 130:110770
TI Biphasic polymerization pr cess using hydrolysis-sensitive monomers
IN Kemnitzer, John E.; Brode, George L.; Kohn, Joachim B.
PA Integra Lifesciences I, Ltd., USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9900442	A1	19990107	WO 1998-US13657	19980629
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9881786	A1	19990119	AU 1998-81786	19980629
EP 991693	A1	20000412	EP 1998-931748	19980629
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, NL, SE, IE, FI				

PRAI US 1997-884108 19970627
WO 1998-US13657 19980629

AB Improvements are disclosed for biphasic polymn. processes in which an aq. soln. of a first monomer that is hydrolytically unstable below a pH of about six or above a pH of about eight is admixed with a water-immiscible org. solvent and there is added to the admixt. a catalyst selected from tertiary amine, quaternary amine and phosphonium catalysts, an acid-forming co-monomer for the first monomer, an acid scavenger, after which the resulting ***polymer*** is recovered, wherein the improvement includes providing the aq. soln. at a pH between about six and about eight, and adding to the admixt. the acid-forming co-monomer and the acid scavenger at relative rates effective to maintain the pH of the admixt. between about six and about eight. The catalyst may be added in a molar ratio to the first monomer effective to provide a predetd. wt.-av. or no.-av. mol. wt. for the resulting ***polymer*** . Biphasic polymn. processes for monomers that are not ***pH*** ***sensitive*** are also disclosed.

L18 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2001 ACS
AN 1988:585513 CAPLUS
DN 109:185593
TI Characteristics of iron release from isolated heavy and light ***endosomes***
AU Bakkeren, Dirk L.; De Jeu-Jaspars, Nel M. H.; Kroos, Martin J.; Van Eijk, Henk G.
CS Dep. Chem. Pathol., Erasmus Univ. Rotterdam, Rotterdam, 3000 DR, Neth.
SO Int. J. Biochem. (1988), 20(8), 837-44
CODEN: IJBJBV; ISSN: 0020-711X
DT Journal
LA English
AB ***Endosomes*** were isolated from K 562 cells after 3 min after the endocytosis of a single cohort of transferrin mols. The change in the 125I/59Fe ratio of heavy and light ***endosomes*** , relative to that

of the transferrin used f r labeling the cells, demonstrated release of 59Fe from heavy ***endosomes*** and f both 125I-labeled transferrin and 59Fe from light ***endos mes*** . Incubation f heavy and light ***endosomes*** with bathophenanthr line disulfonate or pyridoxal-isonicotinoyl ***hydraz ne*** (PIH) showed equal ATP-specific Fe release from b th heavy and light ***endosomes*** , but in the presence of a NADH/NAD+ redox couple Fe release from light ***endosomes*** was reduced. Incubation of heavy and light ***endosomes*** with PIH and N-ethylmaleimide did not completely abolish ATP-specific Fe release from heavy and light ***endosomes*** .

L22 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1994:200306 CAPLUS
DN 120:200306
TI Study of the mechanism of interaction of poly(.epsilon.-caprolactone) nanocapsules with the cornea by confocal laser scanning microscopy
AU Calvo, Pilar; Thomas, Charles; Alonso, Maria J.; Vila-Jato, Jose L.; Robinson, Joseph R.
CS Lab. Farm. Galenica, Fac. Farm., Santiago de Compostela, 15706, Spain
SO Int. J. Pharm. (1994), 103(3), 283-91
CODEN: IJPHDE; ISSN: 0378-5173
DT Journal
LA English
AB With the aim of exploring the potential of poly(.epsilon.-caprolactone) (PECL) nanocapsules as drug carriers for ocular administration, the present study examd. the mechanism of interaction of these nanocapsules with the corneal and conjunctival epithelia. In the first stage of this work, corneas were mounted in a perfusion cell, incubated with a suspension of rhodamine 6G-loaded PECL nanocapsules and subsequently obsd. by confocal laser scanning microscopy. Fluorescence signals were only obsd. within the epithelial cells, but not in the intercellular junctions, thus demonstrating the intracellular localization of the fluorescent nanocapsules. To det. whether this penetration could be assocd. with cellular ***lysis*** or ***endocytotic*** uptake, corneas were pretreated with blank nanocapsules and then stained with propidium iodide, a fluorescent dye which distinguishes viable from non-viable cells. Confocal images of the pretreated corneas did not display any fluorescence signal, thus indicating that PECL nanocapsules penetrate the corneal epithelial cells by an ***endocytotic*** mechanism. In the second stage of the work, rabbit corneas and conjunctivase were removed after in vivo instillation of the nanocapsule suspension and then analyzed by confocal laser scanning microscopy. The in vivo results corroborated the ***endocytosis*** uptake mechanism of nanocapsules by the cornea. On the other hand, no nanocapsules were obsd. in the conjunctival epithelium, which indicates a selective interaction of the PECL nanocapsules for the cornea vs the conjunctiva. These results suggest the ability of these colloidal carriers to specifically target drugs to the cornea while avoiding systemic drug loss through the conjunctiva. To summarize, PECL nanocapsules are shown to be the first demonstrated targeted corneal drug delivery system. Consequently, they may represent a useful approach to promote corneal penetration while simultaneously reducing conjunctival systemic absorption of drugs. This implies a potential increase in therapeutic effect and a redn. of systemic side effects.

L22 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 2000:756891 CAPLUS
DN 133:325653
TI ***Endosomolytic*** agents and cell delivery systems
IN Langer, Robert S.; Putnam, David A.
PA Massachusetts Institute of Technology, USA
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000063409	A1	20001026	WO 2000-US10605	20000420

W: CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
PRAI US 1999-130362 P 19990421
AB The present invention provides improved cell delivery compns. In particular, the invention provides biocompatible ***endosomolytic*** agents. In a preferred embodiment, the ***endosomolytic*** agents are also biodegradable and can be broken down within cells into components that the cell can either reuse or dispose of. In one aspect, the present invention provides ***endosomolytic*** agents capable of effecting the ***lysis*** of an ***endosome*** in response to a change in pH, and methods for effecting the ***lysis*** of an ***endosome*** . These inventive ***endosomolytic*** agents obviate the need for known agents (i.e., chloroquine, fusogenic peptides, inactivated adenoviruses and polyethyleneimine) that can burst ***endosomes*** and have neg. effects on cells. In another aspect, the present invention provides cell delivery compns. comprising an ***endosomolytic*** component that is capable of effecting the ***lysis*** of the ***endosome*** in response to a change in pH, and an encapsulating, or packaging, component capable of packaging a therapeutic agent to be delivered to cellular or subcellular components.
RE.CNT 8
RE
(1) Baylor College Medicine; WO 9640958 A 1996 CAPLUS
(2) Gen Electric; EP 0732366 A 1996 CAPLUS
(3) Himmelstein K; US 4489056 A 1984 CAPLUS
(4) Liang, E; Biochimica Et Biophysica Acta 1998, V1369(1), P39 CAPLUS
(5) Massachusetts Inst Technology; WO 9942091 A 1999 CAPLUS
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